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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/121,211	07/23/98	SHINOHARA T	B0801/7116

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EXAMINER
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ART UNIT	PAPER NUMBER
1646	12

DATE MAILED: 03/01/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/121,211	Shinohara et al.
Examiner	**Group Art Unit**
David S. Romeo	1646

☒ Responsive to communication(s) filed on *1 Nov 1999*.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *see the attached detailed action* is/are pending in the application.

Of the above, claim(s) *see the attached detailed action* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1, 3-11, and 26* is/are rejected.

☒ Claim(s) *2* is/are objected to.

☒ Claims *see the attached detailed action* are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *6*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Disposition of Claims

☒ Claims 1-22, 26, 29, 31, 34, 35, 44, 45, 47, 49, 52, 55, 56, 58, 61, 64, and 70 is/are pending in the application.

Of the above, claim(s) 12-22, 29, 31, 34, 35, 44, 45, 47, 49, 52, 55, 56, 58, 61, 64, and 70 is/are withdrawn from consideration.

☒ Claims 1-22, 26, 29, 31, 34, 35, 44, 45, 47, 49, 52, 55, 56, 58, 61, 64, and 70 are subject to restriction or election requirement.

1. The Office action mailed 01/24/00 (Paper No. 10) is withdrawn. A new Office action follows, wherein new rejections have been inserted into the prior Office action prior to the conclusion.

2. Applicant's election of group I, claims 1-11 and 26, in Paper No. 9 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

3. Claims 12-22, 29, 31, 34, 35, 44, 45, 47, 49, 52, 55, 56, 58, 61, 64, 70 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b) as being drawn to a non-elected invention. Election was made **without** traverse in Paper No. 9.

4. Claims 1-11, 26 are being examined. Claim 26 is being examined only to the extent that it reads upon an agent that is a nucleic acid molecule.

5. This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed.

6. The drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they include the following reference sign(s) not mentioned in the description: 11, 15, 17, 19, 21. Correction is required.

Claim Rejections - 35 USC § 112

7. Claims 1, 8, 10, 26 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification discloses SEQ ID NO:1 which corresponds to the nucleic acid sequence encoding the human species of the LEDGF protein, SEQ ID NO:2. This SEQ ID NO: meets the written description and enablement provision of 35 U.S.C. 112, first paragraph. However, the claims are directed to or encompass sequences that hybridize to SEQ

ID NO:1, corresponding sequences from other species, mutated sequences, allelic variants, splice variants, sequences that have a recited degree of identity, similarity, or homology, and so forth. None of these sequences meets the written description provision of 35 U.S.C. 112, first paragraph.

Vas-Cath Inc. v. Mahurkar , 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (see Vas-Cath at page 1116).

With the exception of SEQ ID NO:1, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides and therefore conception is achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not achieved. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGFs were found unpatentable due to

lack of written description for the broad class. The specification provided only the bovine sequence.

In re Clarke, 148 USPQ 665 (CCPA 1966) held that:

> "It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. In re Soll, 25 C.C.P.A. (Patents) 1309, 97 F.2d 623, 38 USPQ 189; In re Wahlforss et al., 28 C.C.P.A. (Patents) 867, 117 F.21 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of a small genus such as the halogens, consisting of four species, a reduction to practice of three, or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably large number of reductions to practice would probably be necessary."

In the decision of University of California v. Eli Lilly and Co. (CA FC) 43 USPQ2d 1398 (7/22/1997) the court held that:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966.
>
> An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to

a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606."

Whereas the instant specification provides a detailed description of a particular DNA molecule, SEQ ID NO:1, encoding a particular protein, SEQ ID NO:2, the instant specification does not provide a structural formula which is definitive of all hybridizing DNA molecules and mutated variants thereof that encode a LEDGF protein with the desired activity.

Therefore, only SEQ ID NO:1 but not the full breadth of the claim meets the written description provision of 35 U.S.C. 112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115).

8. Claims 1, 3, 8, 10, 26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:1, does not reasonably provide enablement for nucleic acid molecules which hybridize to SEQ ID NO:1 and encode a lens epithelial cell derived growth factor polypeptide, or for a nucleic acid molecule comprising deletions, additions and substitutions of nucleic acid molecules which hybridize to SEQ ID NO:1 and encode a respective lens epithelial cell derived growth factor polypeptide, or for a fragment of SEQ ID NO:13 without regard to the structure and/or function thereof, or for an agent that binds a nucleic acid molecule. The specification does

not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The specification teaches a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 which encodes a polypeptide comprising the amino acid sequence of SEQ ID NO:2. The claims are drawn to or encompass hybridizing polynucleotides encoding a LEDGF and deletions, additions and substitutions of hybridizing polynucleotides encoding a LEDGF that encodes a respective LEDGF. However, the instant specification does not identify those amino acid residues in the amino acid sequence of a LEDGF which are essential for its biological activity and structural integrity and those residues which are either expendable or substitutable. In the absence of this information a practitioner would have to resort to a substantial amount of undue experimentation in the form of insertional, deletional and substitutional mutation analysis of codons encoding over 500 amino acid residues before they could even begin to rationally design a polynucleotide encoding a functional LEDGF having other than a natural amino acid sequence. The disclosure of a single DNA sequence encoding a single LEDGF with a natural amino acid sequence is clearly insufficient support under 35 U.S.C. § 112, first paragraph, for claims which encompass any and all polynucleotides encoding any and all LEDGFs, including mutants thereof, which are encoded by a DNA which hybridizes to a DNA having that single disclosed sequence under the recited stringency conditions, or are deletional, substitutional, or additional mutants thereof encoding a respective LEDGF. Moreover, there is a lack of predictability in the art. Ngo et al. (W_{10}) teach

that the native structure of a protein is a unique three-dimensional structure into which the protein folds under physiological conditions and all the information necessary to determine the native structure can be contained in the primary amino acid sequence (page 433, full paragraph 1). However, it is not even known whether there exist an efficient algorithm for predicting the structure of a given protein from its amino acid sequence alone (page 492, full paragraph 2).

The current claim limitations are analogous to those of claim 7 of U.S. Patent No. 4,703,008, which were held to be invalid under 35 U.S.C. § 112, first paragraph, for want of enablement in *Amgen Inc. v. Chugai Pharmaceuticals Co. Ltd.*, 18 USPQ 2d, 1016 (CAFC, 3/5/91, see page 1026, section D). In that instance a claim to a nucleic acid molecule encoding a polypeptide having an amino acid sequence sufficiently duplicative of the amino acid sequence of erythropoietin (EPO) so as to have a specified biological activity was held to be invalid under 35 U.S.C. § 112, first paragraph, for want of enablement. This limitation is analogous to the hybridization and the deletion, substitution, addition limitations of the instant claims. The disclosure upon which that claim was based described a recombinant DNA encoding EPO and a few analogs thereof. That disclosure differs from the instant specification because, whereas the instant specification describes a DNA encoding a natural LEDGF, it does not describe even a single variant thereof. The court held that what is necessary to support claims of this breadth is a disclosure sufficient to enable one skilled in the art to carry out the invention commensurate with the scope of the claims. For DNA sequences, that means disclosing how to make and use enough

sequences to justify the grant of the patent protection sought in the instant claims. As indicated, the instant specification is even more limited that the '008 patent because it describes only a single protein and no analogs or mutants thereof and, therefore, provides even less support that the '008 specification for claims of comparable scope and which were held to be invalid in that patent.

There are no limitations to the "fragment" of claim 3. A fragment encompasses a single nucleotide. The instant specification has not told the skilled practitioner how to use a single nucleotide of SEQ ID NO:13 as a probe for LEDGF or for the production of a LEDGF polypeptide or fragment thereof.

The limitation "agent" (claim 26) is analogous to a single means claim of the type disparaged by the court. The problem with the phrase "agent" is that it covers every conceivable means which achieves the desired activity, specifically, selective binding to a nucleic acid molecule, whereas the specification discloses at most nucleic acid molecules. As such, the term "agent" encompasses compounds that are structurally unrelated to nucleic acid molecules. The specification fails to teach the skilled artisan how to make such structurally unrelated compounds that have the desired activity or will perform in the manner instantly disclosed. Furthermore, the instant specification does not identify those structural features of an "agent" which are essential for the desired activity those which are not. In the absence of this information a practitioner would have to resort to a substantial amount of unduly extensive experimentation in the form of random analysis of all "agents" before they could even begin to rationally make a "agent" other

than a nucleic acid molecule. The disclosure of a single species of "agent" is clearly insufficient support under 35 U.S.C. § 112, first paragraph, for claims which encompass any and all "agents".

In view of the breadth of the claims, the limited amount of direction and working examples provided by the inventor, the unpredictability in the art and the quantity of experimentation needed to make or use the invention based on the content of the disclosure, it would require undue experimentation for the skilled artisan to make and use the full scope of the claimed invention.

9. Claim 4-7, 9, 11 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claim is drawn to a fragment of SEQ ID NO:1 that is unique within the human genome. In order to make such a fragment knowledge of all the sequences of the genomes of all humans would be required. The instant specification does not teach the sequences of the genomes of all humans. In order to obtain such information the skilled practitioner would have to sequence the genomes of all humans. Furthermore, this information varies as new humans are born and the genetic material recombines and mutates. The instant specification has not enabled the skilled artisan to obtain the sequences of all the genomes of all humans without undue experimentation. Consequently, claims to a fragment unique within the human genome are not enabled. In the

absence of a knowledge of the sequences of all genomes of all humans or even the knowledge of the sequence of a single genome it is impossible to predict the uniqueness of a nucleotide sequence. In view of the breadth of the claims, the lack of direction and working examples provided by the inventor, the unpredictability in the art and the quantity of experimentation needed to make or use the invention based on the content of the disclosure, it would require undue experimentation for the skilled artisan to make and use the full scope of the claimed invention

10. The following claims are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 8, 10, 26 are indefinite over the recitation of "comprising (a) nucleic acid molecules which hybridize" because it is unclear if the claimed nucleic acid molecule is a chimera comprising the entire universe of hybridizing nucleic acid molecules or if it comprises a single nucleic acid molecule within such a universe. The metes and bounds of the claim(s) are not clearly set forth. It is suggested that the claim recite "a nucleic acid molecule which hybridizes".

Claims 1, 8, 10, 26 are indefinite over the recitation of "stringent conditions" because stringency varies according to the hybridization conditions and the particular hybrid under study. See Sambrook et al. (U_{10}), page 9.50, paragraph 9. The specification fails to precisely define

"stringent conditions". Any degree of stringency is embraced by the claims. One of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

Claims 1, 8, 10, 26 are indefinite over the recitation of "a nucleic acid of SEQ ID NO:1" (claim 1, line 3) because it is unclear if the nucleic acid of SEQ ID NO:1 or some portion thereof is intended. The metes and bounds of the claim(s) are not clearly set forth. It is suggested that the claim recite "the nucleic acid of SEQ ID NO:1".

Claim(s) 1, 4-11, 26 are indefinite because they recite the terms "lens epithelial cell derived growth factor polypeptide" or "respective lens epithelial cell derived growth factor polypeptide". Because the instant specification does not identify that material element or combination of elements which is unique to, and, therefore, definitive of "lens epithelial cell derived growth factor polypeptide" or "respective lens epithelial cell derived growth factor polypeptide" an artisan cannot determine what additional limitations are placed upon a claim by the presence of this term. It is suggested that the claims recite "polypeptide" instead.

Claims 4-7, 9, 11 are indefinite over the recitation of "represent a sequence unique within the human genome" because it is unclear which properties of the claimed nucleic acid molecule are supposed to be unique and which are not. Furthermore, the instant specification does not set forth the human genome and the human genome varies as new individuals are born. The metes and bounds of the claim(s) are not clearly set forth.

Claim 26 is indefinite over the recitation of "control" because the claim does not set forth that material element or combination of elements which is unique to, and, therefore, definitive of a "control" an artisan cannot determine what additional limitations are placed upon a claim by the presence of this term.

Claims 4-7, 9, 11 are indefinite over the recitation of "identifying a nucleic acid molecule encoding a LEDGF" because the nature and extent of the "identification" are unclear. It is unclear if the "identification" is by virtue of hybridization or an encoded polypeptide or a functional activity thereof. The metes and bounds of the claim(s) are not clearly set forth.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

12. Claims 1, 8, 10, 26 are rejected under 35 U.S.C. 102(e) as being anticipated by Fiddes et al. (A_{10}). Fiddes et al. teach an isolated nucleic acid molecule encoding bFGF (column 4, lines 38-41), an expression vector comprising the nucleic acid molecule operably linked to a promoter, and a host cell transformed with the expression vector (column 11, line 6, through column 14, line 55; column 19, line 10, through column 25, line 33). The isolated nucleic acid molecule comprises

deletions, additions and substitutions of nucleic acid molecules which hybridize to SEQ ID NO:1 and it encodes a respective lens epithelial cell derived growth factor polypeptide. The isolated nucleic acid molecule is also an agent that binds to a nucleic acid molecule comprising deletions, additions and substitutions of nucleic acid molecules which hybridize to SEQ ID NO:1, and it is a control for comparing a measured value of binding.

New Objection-Specification

13. The attempt to incorporate subject matter into this application by reference to GenBank accession numbers (Table III) is improper because the nucleotide sequences are critical or essential material to the practice of the invention. "Essential material" is defined as that which is necessary to (1) describe the claimed invention, or, in the instant case what the claimed invention is not. In any application which is to issue as a U.S. patent, essential material may not be incorporated by reference to (1) patents or applications published by foreign countries or a regional patent office, (2) non-patent publications, (3) a U.S. patent or application which itself incorporates "essential material" by reference, or (4) a foreign application.

The incorporation of essential material in the specification by reference to a foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner

representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. In re Hawkins, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); In re Hawkins, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); In re Hawkins, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

New Claim Rejections - 35 USC § 112

14. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 4-7, 9-11 are rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure which is not enabling. The nucleotide sequences of the GenBank accession numbers critical or essential to the practice of the invention, but not included in the claim(s) are not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976). The attempt to incorporate subject matter into this application by reference to GenBank accession numbers is improper because mere reference to a publication is not an incorporation of anything into the application. The statement at page 56, line 5, has been interpreted to mean that the GenBank accession numbers are incorporated by reference. Applicant is required to amend the specification to include the sequences incorporated by reference because the sequences are essential material. See MPEP § 608.01(p). Applicant must establish that the sequences added by amendment are the

sequences present in the GenBank data base as of the filing date of the application. This is because if GenBank sequences are amended and accession numbers do not change, the metes and bounds of the invention may change. A sequence previously meant to be excluded at filing may no longer be excluded, or a sequence not previously meant to be excluded may become excluded. If applicant chooses to amend the specification by inserting the sequences corresponding to the accession numbers, the inserted sequences must comply with the sequence rules. Applicant must establish that the inserted sequences were identical to those in the GenBank listings as of the filing date of the application.

15. The following claims are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 4-7, 9-11 are indefinite because they refer to GenBank accession numbers. Revisions or updates to GenBank entries can be made at any time. The interpretation of a claim that refers to a GenBank entry is dependent upon the particular revision, update or release date of that particular entry. Since GenBank accession numbers may not change when GenBank sequences are amended, one would not know the precise nucleic acid sequences associated with the accession numbers at the time the application was filed. The metes and bounds of the claim(s) are not clearly set forth.

Conclusion

16. Claim 2 is objected to as being dependent upon a rejected base claim. SEQ ID NOs:1 and 13 are free of the prior art of record.

17. The art made of record and not relied upon is considered pertinent to applicant's disclosure. Database Medline accession no. 1999366075 (V_{10}) teaches that bFGF is a respective lens epithelial cell derived growth factor polypeptide (Abstract).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David S. Romeo whose telephone number is (703) 305-4050. The examiner can normally be reached on Monday through Friday from 6:45 a.m. to 3:15 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4242.

Faxed draft or informal communications should be directed to the examiner at (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

DAVID ROMEO
PATENT EXAMINER
February 28, 2000